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Health and Environmental Effects Profile for Vernolate

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR VERNOLATE

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16. ABSTRACT

The Health and Environmental Effects Profile for vernolate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Vernolate has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for vernolate is 5×10^{-2} (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT	3
2.1.	AIR	3
2.1.	WATER	3
2.3.	SOIL	4
3.	EXPOSURE	7
4.	PHARMACOKINETICS	8
4.1.	ABSORPTION	8
4.2.	DISTRIBUTION	8
4.3.	METABOLISM	8
4.4.	EXCRETION	8
5.	EFFECTS	9
5.1.	CARCINOGENICITY	9
5.2.	MUTAGENICITY	9
5.3.	TERATOGENICITY	11
5.4.	OTHER REPRODUCTIVE EFFECTS	11
5.5.	CHRONIC TOXICITY	11
5.6.	OTHER RELEVANT INFORMATION	11
6.	AQUATIC TOXICITY	12
6.1.	ACUTE TOXICITY	12
6.2.	CHRONIC EFFECTS	12
6.3.	PLANT EFFECTS	12
6.4.	RESIDUE	12
6.5.	OTHER RELEVANT INFORMATION	12
7.	EXISTING GUIDELINES AND STANDARDS	14
7.1.	HUMAN	14
7.2.	AQUATIC	14
8.	RISK ASSESSMENT	15
9.	REFERENCES	16
	APPENDIX: LITERATURE SEARCHED	21

LIST OF TABLES

No.	Title	Page
5-1	Mutagenicity Testing of Vernolate	10
6-1	Acute Toxicity of Vernolate to Aquatic Animals.	13

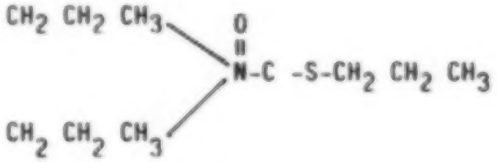
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Vernolate is the common name for S-propyl dipropylthiocarbamate (BCPC, 1977). It is also known as S-propyl dipropylcarbamothioate (BCPC, 1977); carbamic acid, dipropylthio-, S-propyl ester; dipropylthiocarbamic acid S-propyl ester; PPTC; propyl N,N-dipropylthiolcarbamate; n-propyl-di-n-propylthiolcarbamate; and S-propyl dipropylthiocarbamate (NIOSH, 1983). This compound was introduced to the market in 1954 by Stauffer Chemical Company under the code number "R-1607" and has a trade name of "Vernam" (BCPC, 1977). The structure of vernolate is given below:



The molecular formula for this compound is $C_{10}H_{21}NOS$ and its molecular weight is 203.3. The Chemical Abstract Service (CAS) Registry Number for vernolate is 1929-77-7.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Vernolate is a clear liquid with an aromatic odor at ambient temperature. Some of the physical properties of vernolate, as summarized by BCPC (1977), are given below:

Boiling Point:	150°C at 30 mm Hg
Vapor Pressure at 25°C:	10.4×10^{-3} mm Hg
Density at 20°C:	0.954 g/cm³
Solubility in water at 21°C:	107 mg/ℓ
Solubility in organic solvents:	miscible with common organic solvents, including kerosene, isobutyl methyl ketone and xylene

1.3. PRODUCTION DATA

Vernolate is prepared by the reaction of dipropylcarbamoyl chloride with propane-1-thiol (BCPC, 1977) or by the reaction of n-propyl chlorothiolformate with di-n-propylamine (SRI, 1976). Vernolate is produced by Stauffer Chemical Company, Agricultural Chemicals Division, Cold Creek, AL (SRI International, 1983). Recent production data for the United States are unavailable, but the estimated yearly production of vernolate for 1971 was 2 million pounds (Lawless et al., 1972).

1.4. USE DATA

Vernolate is used as a pre-emergence herbicide to control weeds in soybeans, peanuts, sweet potatoes and tobacco crops (BCPC, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

There are only limited data regarding the fate and transport of vernolate in air. The important route of entry into the atmosphere is through volatilization from soil. Gray and Weierich (1968a) reported that 64 days after soil incorporation of vernolate at 6.0 pounds/acre on moist (15.4% moisture) Felton loamy sand and Sorrento loam at 70-80°F, 93 and 86%, respectively, was volatilized. Volatilization was affected by moisture content of the soil, temperature and soil type.

The fate of vernolate in the air is likely to be determined by its ability to react with O_3, NO_x, and free radicals (e.g., RO•, O• and RO_2•) and by its ability to undergo photochemical reaction. The probability of chemical or photochemical reactions of vernolate in the atmosphere has not been investigated.

2.2. WATER

There are only limited data regarding the fate and transport of vernolate in aquatic media. Based on its volatility from moist soil, it is likely that significant volatilization of vernolate from aquatic media will take place. Although the rates of microbial degradation of vernolate in aquatic media have not been determined, based on its biodegradability in soils (Smith and Fitzpatrick, 1970; Gray and Weierich, 1968a; Corbin and Upchurch, 1967), it is possible that biodegradation may be a significant process in determining the fate of vernolate in aquatic media.

Smith and Fitzpatrick (1970) examined the hydrolysis of vernolate in acidic and basic solutions. In 29N H_2SO_4 solution, the hydrolysis half-life for vernolate was 1 hour at 75°C. Vernolate was stable in basic solution, with negligible hydrolysis (<10%) occurring in 10N NaOH even at 95°C

for 1 hour. Smith and Fitzpatrick (1970) concluded that hydrolysis of vernolate can only occur in highly acidic solutions at the thiolcarbamate linkage, resulting in a secondary amine as the hydrolysis product. Therefore, it is likely that vernolate will not undergo hydrolysis in natural soils where the pH is not low enough for the hydrolysis reaction to proceed.

No experimental data regarding the bioconcentration of vernolate by aquatic organisms are available. From binary regression equations, Kenaga (1980) predicted a BCF of 44 based on the water solubility (Section 6.4.). Therefore, this compound is not expected to be significantly bioaccumulated in aquatic organisms.

2.3. SOIL

The fate and transport of vernolate have been studied most extensively in soil. The major process for removal of vernolate from wet soil is volatilization. Soil conditions that affect volatilization of vernolate were examined by Gray and Weierich (1968a). Volatilization of vernolate from dry (1% moisture) or moist (14% moisture) Santa Cruz loamy sand increased over the temperature range of 32-80 and 32-60°F, respectively. Gray and Weierich (1968a) also examined the effects of temperature and moisture on volatilization of vernolate from two different soil types. After 64 days in moist soil at 70-80°F, vernolate volatilization was 93 and 86% from Felton loamy sand and Sorrento loam, respectively, while losses after 64 days in both types of moist soils at 40°F were much less (42 and 39%, respectively). After 64 days, 14% of the applied vernolate was volatilized from both types of dry soil at 80°F. The lower volatility in dry soil was concluded to be due to stronger adsorption in dry soil. Thus, increase in both temperature and soil moisture contents increases the volatility of vernolate from soils.

Microbial degradation of vernolate also appears to be an important mechanism for removal of vernolate from soil. In a laboratory study, vernolate was biotransformed more quickly in nonautoclaved soils as compared to sterile, autoclaved soils, indicating that microbial degradation was an important process in the transformation of vernolate (Gray and Weierich, 1968a). Smith and Fitzpatrick (1970) reported a degradation half-life of 2-3 weeks in two types of nonsterile soils, Regina heavy clay and Weyburn loam. Corbin and Upchurch (1967) applied 1280 ppm of vernolate to two soils high in organic matter at pH 4.3, 5.3, 6.5 and 7.5. Bacteria-mediated vernolate degradation of 60% was achieved within 8 weeks at an optimum pH of 7.5; lesser biotransformation was observed at lower pH.

Leaching of vernolate from soil does not appear to be an important mechanism for removal. Gray and Weierich (1968a,b) examined the possibility of vernolate leaching in Santo Cruz loamy sand, coyote sandy loam, Sorrento loam, Bower's clay, and Egbert peat; the clay content of these soils ranged from 5.0-33.2%, and the organic matter content ranged from 0.8-34.6%. In all five soil types, vernolate was relatively resistant to leaching within 16 hours after application at a level of 10 pounds/acre in the top 2 inches of soil. Increasing clay and organic matter content of the soil resulted in an accompanying decrease in the amount of leaching. Using soil columns, Harris (1967) studied the effects of soil types on the movement of vernolate in soil. In a comparison based on a scale of 1-6 regarding the mobility of 28 herbicides in soil, vernolate was observed to have a mobility of 2.2 in Hagerstown silty clay loam and of 2.3 in Lakeland sandy loam. These results support the calculated K_{oc} (soil adsorption coefficient) of 330, indicating only slight mobility of vernolate in soil (Kenaga, 1980).

In a field study, Burnside and Schultz (1978) applied vernolate as a preplant incorporation at 3.4 kg/ha. Vernolate residues were not effective in controlling weeds during the 2 years following application. Therefore, the authors concluded that vernolate would not persist from one growing season to another.

3. EXPOSURE

STORET contains no monitoring data for vernolate. Kawahara et al. (1971) reported residues of <0.01 ppm of vernolate in tomato and strawberry products 55 days after the herbicide was applied.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of vernolate were not located in the available literature.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of vernolate were not located in the available literature.

4.3. METABOLISM

Casida et al. (1975) reported that vernolate was oxidized *in vitro* to the corresponding thiocarbamate sulfoxide by the mouse hepatic microsome-NADPH system. The resulting sulfoxide was then cleaved by the hepatic soluble-glutathione S-transferase system. Casida et al. (1975) also examined the *in vivo* metabolism of vernolate following intraperitoneal injection of 1 or 2 mmole/kg to Swiss-Webster mice. The corresponding thiocarbamate sulfoxide was reported to be a transient hepatic metabolite of vernolate; however, corresponding thiocarbamate sulfones were not detected as *in vivo* metabolites of vernolate. The authors concluded that sulfoxidation is the initial metabolic step in the cleavage of the thiocarbamate ester group and in the detoxification of vernolate in mice.

4.4. EXCRETION

Pertinent data regarding the excretion of vernolate were not located in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of vernolate were not located in the available literature. This compound is not scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

The genotoxicity of vernolate has been tested in various bacteria, Drosophila, and mammalian assays. These mutagenicity tests are summarized in Table 5-1.

Negative results were obtained for vernolate in reverse mutation assays with Salmonella typhimurium both in the presence and absence of a mammalian metabolic activation system (Andersen et al., 1972; Eisenbeis et al., 1981; Shirasu et al., 1976) and with Escherichia coli (Shirasu et al., 1976). Vernolate also gave negative results in the rec-assay with repair deficient and proficient strains of Bacillus subtilis (Shirasu et al., 1976).

Vernolate was reported in a meeting abstract to significantly increase the frequency of sex-linked recessive lethals but not dominant lethals in Drosophila melanogaster (Murnik, 1976).

Pilinskaya et al. (1980a,b) administered a single intragastric dose of vernolate at a level of 0.2-0.5 of the LD_{50} (actual dose not reported) to albino mice, and examined the bone marrow cells of treated animals for chromosome aberrations. Positive cytogenetic or mutagenic activity of vernolate was reported, as determined by a significantly increased frequency of aberrant metaphases in the bone marrow cells of treated animals. No additional information was presented in the available abstract of this Russian study.

TABLE 5-1

Mutagenicity Testing of Vernolate

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium 8 histidine-deficient strains NR	spot test	NR	None	-	NC	Andersen et al., 1972
Reverse mutation	S. typhimurium TA98 TA100 TA1535 TA1537 TA1538	spot test	crystals of compound; concentration NOS	±S9	 - - - - -	NC	Eisenbeis et al., 1981
Reverse mutation	S. typhimurium TA1535 TA1536 TA1537 TA1538	spot test	NR	None	 - - - -	NC	Shirasu et al., 1976
Reverse mutation	Escherichia coli B/r try WP2 WP2 try hcr	spot test	NR	None	 - -	NC	Shirasu et al., 1976
Rec-assay	Bacillus subtilis H17 rec$^+$ M45 rec$^-$	spot test	NR	None	 - -	NC	Shirasu et al., 1976
Sex-linked recessive lethal	Drosophila melanogaster	NR	NR	None	+	NC	Murnik, 1976
Dominant lethal	D. melanogaster	NR	NR	None	-	NC	Murnik, 1976
Chromosome aberration	albino mice	single intragastric administration	0.2-0.5 of the LD_{50} (dose NOS)	None	+	cytogenetic or mutagenic activity was determined by a significantly increased frequency of aberrant metaphases in bone marrow cells of treated animals	Pilinskaya et al., 1980a,b

NR = Not reported; NC = No comment; NOS = Not otherwise specified

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of vernolate were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of vernolate were not located in the available literature.

5.5. CHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of vernolate were not located in the available literature.

5.6. OTHER RELEVANT INFORMATION

Karpenko (1981) administered both single and repeated doses (dose levels, route of exposure, and duration of exposures not reported) of vernolate to rats and cats. A single administration of vernolate resulted in hypocoagulation within 3-4 hours after treatment, whereas prolonged exposure resulted in a hyper-hypocoagulation syndrome that was characterized by hypercoagulation during the first few days after administration and hypocoagulation over the remainder of administration (duration not reported). This Russian study was only available in abstract form; therefore, the complete details of experimental design and effects were not provided.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Acute toxicity tests of vernolate have been conducted with at least seven species of freshwater invertebrates and four species of freshwater fish (Table 6-1). Acute LC_{50} values ranged from 0.23 mg/ℓ for aquatic sowbugs, Asellus brevicaudus, to 24 mg/ℓ for crayfish. Acute toxicity tests of vernolate at 1 mg/ℓ have also been conducted by Butler (1965) with three species of marine animals. Exposure to 1 mg/ℓ had no effect on spot, Leiostomus xanthurus (a fish species), after 48 hours and no effect on shell growth of oysters, Crassostrea virginica, during 96 hours of exposure. In contrast, exposure to 1 mg/ℓ for 48 hours caused 20% mortality in adult brown shrimp, Penaeus aztecus.

6.2. CHRONIC EFFECTS

Pertinent data regarding chronic effects of vernolate on aquatic animals were not located in the available literature.

6.3. PLANT EFFECTS

The only information regarding the effects of vernolate on aquatic plants was the report by Nishiuchi (1975) who found that the growth of duckweed, Lemna paucicostata, was not affected by treatment at 100 ppm vernolate.

6.4. RESIDUE

Pertinent data regarding vernolate residues in aquatic organisms were not located in the available literature. Kenaga (1980) reported a BCF of 44 calculated from water solubility (107 mg/ℓ) by regression equations.

6.5. OTHER RELEVANT INFORMATION

Other relevant data regarding the effects of vernolate on aquatic organisms were not located in the available literature.

TABLE 6-1

Acute Toxicity of Vernolate to Aquatic Animals

Species	LC_{50} (mg/ℓ) 48-hour	LC_{50} (mg/ℓ) 96-hour	Reference
Water flea *Daphnia magna*	1.1	NR	Sanders, 1970
Seed shrimp *Cyridopsis vidua*	0.24	0.25	Sanders, 1970; Johnson and Finley, 1980
Scud *Gammarus fasciatus*	18	13	Sanders, 1970
Scud *Gammarus lacustris*	NR	1.8	Sanders, 1969
Sowbug *Asellus brevicaudus*	5.6	0.23	Sanders, 1970; Johnson and Finley, 1980
Glass shrimp *Palaemonetes kadiakensis*	1.9	0.53	Sanders, 1970; Johnson and Finley, 1980
Crayfish *Orconectes nails*	24.0	NR	Sanders, 1970
Rainbow trout *Salmo gairdneri*	NR	4.3-9.0	Johnson and Finley, 1980 Schneider, 1979
Goldfish *Carassius auratus*	NR	12.7	Schneider, 1979
Three-spined stickleback *Gasterosteus aculeatus*	NR	1-10	Pimentel, 1971
Bluegill *Lepomis macrochirus*	NR	2.5-12.5	Johnson and Finley, 1980 Schneider, 1979

NR = Not reported

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Under the Federal Food, Drug, and Cosmetic Act, a tolerance of 0.1 ppm has been established for vernolate residues in or on potatoes (Federal Register, 1971); in or on the feed ingredient peanut hulls (Federal Register, 1981); in or on peanuts, peanut forage and hay, soybeans, soybean forage and hay, and sweet potatoes (Federal Register, 1968); in or on corn grain, fodder and forage, and fresh corn including sweet corn [Federal REgister, 1972).

Aleksandrova and Klisenko (1982) reported the Russian maximum allowable concentration for vernolate in air of 5.0 mg/m^3.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of vernolate were not located in the available literature.

8. RISK ASSESSMENT

No carcinogenicity assays or chronic toxicity studies of vernolate were located in the available literature. Vernolate significantly increased the frequency of sex-linked recessive lethals in Drosophila melanogaster (Murnik, 1976) and of aberrant metaphases in the bone marrow cells of orally treated mice (Pilinskaya et al., 1980a,b), but was negative in reverse mutation assays with Salmonella typhimurium (Andersen et al., 1972; Eisenbeis et al., 1981; Shirasu et al., 1976) and Escherichia coli (Shirasu et al., 1976) both in the presence and absence of a mammalian metabolic activation system, and in the rec-assay with repair deficient and proficient strains of Bacillus subtilis (Shirasu et al., 1976). No information regarding the potential teratogenicity of vernolate was available. Karpenko (1981) reported hypercoagulation in rats and cats as a result of a single exposure to vernolate and hypercoagulation followed by hypocoagulation upon prolonged exposure; however, the available abstract of this Russian study lacked information regarding dose levels, duration of exposures and other toxicological endpoints evaluated.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data from which an ADI of 0.05 mg/kg bw/day or 3.5 mg/day for a 70 kg human was derived. The ADI was based on a NOEL of 5 mg/kg bw/day in rats in a 1-year feeding

study and an uncertainty factor of 100 (10 to account for interspecies extrapolation and 10 for protection of the most sensitive individuals within the human population). The subchronic LOAEL for impaired blood clotting and hemorrhage was 20 mg/kg bw/day in rats.

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APPENDIX:

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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